EXPERIMENTAL STUDIES WITH THE DERMATOPHYTES

III. Development and Duration of Immunity and Hypersensitivity in Guinea Pigs

EDWARD D. DeLAMATER*

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A. INTRODUCTION

Summaries of the pertinent literature on experimental ringworm in various laboratory animals have been given in previous papers (1, 2). Experimental data on many aspects of the problem were presented at the same time. The experiments and results to be described here are a logical sequence of the results already published. This work was begun and has been continued with the idea of determining, if possible, which of the results of the previous investigators were the salient ones, and how their conflicting data could be fitted into an understandable pattern and so be explained. It is believed that this has been achieved at least in part. The essential features of such a pattern based on experimental data were presented in 1939 (3), and more recently Sulzberger (4) has emphasized and expanded on the same outline.

B. METHODS USED

Infection (both first inoculations and reinoculations) was accomplished by simply rubbing fungus material from Sabouraud's honey agar cultures into scarified skin areas about the size of a fifty cent piece. Scarification was done by scraping the skin with a scalpel after the hair had been removed with fine clippers.

* Department of Dermatology, College of Physicians and Surgeons, Columbia University, New York City, 1940.

The presence of fungi was determined by direct microscopic examination of material removed from the lesions. This method has been found to be more accurate than the use of cultures. Determinations were done every 4 or 5 days.

Tests for hypersensitivity were done by intradermal injection of 0.2 cc. of fungous extracts prepared by the method of Bishop (2) and standardized by determining the total nitrogen content of the extract and diluting this so that solutions for testing contained 1.0 mgm. of nitrogen per 100 cc. of solution. It is recognized that the nitrogen content may not be a valid standard, but until more is known of the chemistry of the active agents, this seems to be the best method of standardization available.

Trichophyton gypseum (strain # 108), isolated from a squirrel (5), has been used in all experiments. Only guinea pigs weighing between 250–300 grams were used.

C. THE PRIMARY DISEASE

The clinical course of ringworm in guinea pigs has been well established. Through the work of many authors (1 and 2) it is clearly divisible into four rather distinctive phases. These are as follows:

1. The period of incubation, which lasts 4 to 6 days.
2. The period of spread, which lasts until the 12th to 15th day.
3. The climax, extending from the 12th to the 15th day, and representing the point of reversal in the progress of the disease.
4. The period of clearing and healing which runs from the climax until the lesion is healed at between the 32nd and the 39th day.

With this brief outline of the course of the clinical disease, it will now be possible to relate more understandably the development of the allergic and immunologic phenomena which are a part of it.

D. DEVELOPMENT OF HYPERSENSITIVITY (ALLERGY) DURING THE PRIMARY DISEASE

To test for the presence and development of sensitivity during the course of the disease to the specific fungus involved (*T.*

gypseum) extracts of the fungus were injected in 0.2 cc. doses intradermally approximately every third day during the clinical course of the experimental infection and for a period thereafter. The degree of allergy was measured by the size and duration of the papule produced. It is interesting to note that the papule reaches its maximum size in the disease course before its period of longest duration. Chart 1 demonstrates specific cases of the development of allergic reactions to test doses of fungous extracts during the course of the primary infection. The following conclusions may be drawn:

1. No reaction occurs in normal uninfected animals.

CHART 1

Rise of sensitization during normal primary infection

	Day before infection	1st test 1st day	2nd test 3d day	3d test 7th day	4th test 11th day	5th test 15th day	6th test 18th day	7th test 26th day	8th test 31st day	9th test 41st day	10th test 51st day	11th test 65th day	12th test 80th day
Number of animals	25	25	25	25	25	25	25	25	25	25	24	24	24
Papule size (cm)	0	0	0–±	0–±	–1–1	1+	1+	1½–2	1½+–2	2	1½+–2	1½	1+
Duration of papule (days)	0	0	0	0	3–6	7–10	9–10	9–11	11	11	12–16	10–13	10

* End of clinical course, ± 35th day.

2. None, or very slight reactions only, occur during the period of incubation (4th to 7th day).
3. Reactions begin at about the time the period of spread is initiated, which corresponds to the first appearance of an inflammatory reaction in the lesion.
4. Reactions to successive tests become more intense as the lesion progresses.
5. The greatest intensity of the reactions is not reached until two to three weeks after the disease has cleared, at which time it begins to fall off.

The development of an allergy to the invading fungus parasite, as demonstrated by the injection of test doses of extracts and by the intense reaction produced at sites of reinoculation is highly

characteristic of the disease. It is found to correspond closely to what is known to occur in non-lethal infections with the tubercle bacillus, as has recently been emphasized by Sulzberger (4).

E. DEVELOPMENT OF IMMUNITY DURING THE PRIMARY DISEASE

An immunity, demonstrable by reinoculation of the fungus into previously infected animals, is developed during the first infection in close conjunction with the allergy to fungus extracts just

CHART 2

Comparison of the primary disease and reinoculations done during the course of the primary disease; showing the development of immunity during the course of the primary disease

	CONTROL—NO PREVIOUS INOCULATIONS	SIMULTANEOUS INOCULATIONS	REINOCULATION DURING EARLY SPREAD (5TH DAY)	CLIMAX (13TH DAY)	EARLY CLEARING (26TH DAY)	LATE CLEARING (34TH DAY)	AFTER RECOVERY 40TH DAY	
							Ipsilateral	Contralateral
Number of animals...	10	4	3	5	5	5	23	23
Time of reinoculation after primary (days).....	0	0	5	13	26	34	40	40
Peak of reaction (days).....	12–15	12–15	7–8	2–3	2–3	2–3	2	2–4
Intensity of inflammation.....	+	+	+	++	++–+++	++	+	+++
Duration of infection (days).....	32–39	32–39	26–28	12–13	12–13	11–13	7–9	13–17
Persistence of fungi (days).....	19–30	19–30	13	0–7	0–5	0–5	0	0–8
Degree of crusting...	++	++	++	+++	+++	++	+	+++

described. By reinoculating animals during the different phases of the first infection, it is possible to produce secondary diseases of modified character and duration. Chart 2 summarizes results of reinoculations done 5, 13, 26, 34 and 40 days after the primary inoculation. The disease process produced in each of these cases is modified both as to intensity and duration as well as with respect to the length of time the fungi persist in them. The presence or absence of fungi in the lesions can be taken as a direct index of the presence or absence of immunity and of its degree.

The intensity of the tissue reactions is a further indicator of the sensitivity of the tissue to the presence of the fungi, their products, or both.

The following conclusions may be drawn from these experiments:

1. Simultaneous inoculations on opposite sides of the animal give identical disease pictures.

2. Reinoculations done during or just after the period of incubation of the primary infection (5 days), take, producing an active but abbreviated infection. The course is shortened or telescoped, all phases of the disease being affected. The disease lasts only 26 to 28 days as against 32 to 39 days in the normal. The fungi persist in the lesion for 13 days as against 20 to 30 days in the normal.

This demonstrates an increased resistance to infection.

3. Reinoculations during climax (13th day) of the primary infection suffer further interference. They persist for only 12 to 13 days; are very inflammatory and scaly. Sixty per cent of the cases show no fungi to be present. In the other 40 per cent the fungi only persist for about seven days as contrasted to 20 to 30 days in the normal. Here is clear cut resistance to reinfection, 60 per cent showing complete immunity, 40 per cent partial immunity.

4. Reinoculations done on the 26th day show an even more intense inflammatory reaction to the presence of the fungi although the disease lasts the same length of time (12 to 13 days). The fungi persist in the lesions for an even shorter time, when they are present at all, indicating an increasing immunity.

5. Reinoculations done on the 34th day after the primary inoculation show a slightly decreased duration, slightly decreased inflammatory response, and decreased tendency to scale. The various aspects of this picture can be modified by the place at which the reinoculation is done, as will be demonstrated presently. Resistance to infection is about the same as in the previous cases.

6. Reinoculations done on the 40th day after the beginning of the primary disease, demonstrate clearly the influence of the skin area into which the reinoculation is done.

I. Reinoculations done in the area of previous infection show: (a) A further reduction of the duration of the reinoculation disease. (b) A further decrease of inflammatory response and the accompanying scaling of the lesion. (c) Complete immunity, in contrast to the partial immunity described above, as shown by the total absence of proliferating fungi in the lesion.

II. Reinoculations done in previously uninfected skin areas in contrast show: (a) Almost double the duration of the pathologic process. (b) Greater inflammatory response with greater scaling of the lesion associated with it. (c) A generalized immunity to occur in approximately 50 per cent of the animals, as shown by complete absence of proliferating fungi in the lesions,

CHART 3

Duration of sensitivity reactions after healing of the primary infection

	1ST TEST	2ND TEST	3RD TEST	4TH TEST	5TH TEST	6TH TEST	7TH TEST	8TH TEST	9TH TEST
	Time of testing after primary								
	2-4 days	1 week	2 weeks	1 month	6 weeks	2 months	3 months	5 months	6 months
Number of cases....	24	24	23	26	22	3	5	3	1
Size of papule (cm.).	1½–2	1½+–2	1½	1+	1	±1	±1	−1	−1
Duration of papule (days)	10–11	11–12	11–13	8–10	5–7	8–9	7–8	4–6	6

while the other 50 per cent of the animals show only a partial immunity (varying somewhat in degree) as shown by the presence of actively proliferating fungi in the lesions for short periods, ranging up to eight days. A further consideration of this phenomenon will be given presently.

F. DURATION OF HYPERSENSITIVITY (ALLERGY) AFTER THE PRIMARY INFECTION

Tests for the duration of the hypersensitivity (allergy) produced by the primary lesion were done by the usual 0.2 cc. test injections of fungous extracts at intervals after the primary disease had cleared. These reactions are tabulated in chart 3.

The following conclusions may be drawn from these data:

1. The sensitivity continues to rise for a period of two to three weeks after the primary disease process has cleared.
2. After reaching its peak the hypersensitivity gradually decreases over a period of months as shown by the reduction in the size and duration of the papular response.

This decrease in the allergic reactions is associated with a corresponding decrease in the immunity, which, it has been seen, develops concurrently with the hypersensitivity during the course of the primary infection.

G. DURATION OF IMMUNITY AFTER PRIMARY INFECTION AS SHOWN BY REINOCULATIONS

Reinoculations were done in a manner similar to the first inoculations, at intervals up to eleven months after the primary infection had cleared. All reinoculations considered here were done in the skin areas which had *not* been previously infected, so that the local phenomena associated with previously infected areas are not to be considered here. The results apply to the more general immunity of the animals.

Reinoculations done during the first and second months after healing of the primary lesion give the same results as those done immediately following the primary lesion. The lesions persist from 12 to 15 days, and are relatively very inflammatory with intense exfoliation. The presence of fungi (in approximately 50 per cent of cases) is of short duration (3 to 8 days) or is completely absent (50 per cent).

Reinoculations done during the $2\frac{1}{2}$ to $3\frac{1}{2}$ month interval show a reduction of the duration with a corresponding reduction of the inflammatory processes in the lesion. This also corresponds with the decline of the papular response to test injections of extracts.

Reinoculations done during the five to six month interval show some cases which parallel those just described (a); while others (b) show an increased inflammatory response and an increased duration of the disease up to 27 days.

Fungi are present from 12 to 15 days and the infection simulates closely those produced by reinoculation done early during

the course of the first infection. Other cases (c) completely parallel the first infectious disease.

Reinoculations done during the 8 to 11 month interval are similar in all respects to the last two types of reinfection (b and c) just described for the five to six month interval.

These data demonstrate the gradual loss of immunity to reinfection as the interval since the primary lesion lengthens.

CHART 4

Duration of immunity after first infection as shown by reinoculation

	PERIODS AT WHICH REINOCULATION DONE				
	Control, primary infection	0–2 month interval	2–3½ month interval	5–6 month interval	8–11 month interval
Duration of lesions (days).....	32–39	12–18	12–15	14–16 (a) 24–27 (b) 32–35 (c)	22–24 (a) 32–35 (b)
Persistence of fungi in lesions (days)..	19–30	0–6	0–6	0 (a) 12–18 (b) 19–30 (c)	12–18 (a) 19–30 (b)
Degree of inflammatory response in lesions.....	++	++–+++	+	+ (a) ++ (b) ++ (c)	++ (a) ++ (b)
Number of animals.	139	15	35	2 (a) 3 (b) 4 (c)	2 (a) 8 (b)

It will be readily seen that there is a close correlation between this loss of immunity and the decline of hypersensitivity demonstrated above.

H. CLINICAL DESCRIPTION OF THE COURSE OF REINOCULATION DISEASE AND THE FACTORS MODIFYING IT

The clinical course of reinoculation disease can be made to vary, as has already been pointed out, by the influence of: 1)

The skin area onto which reinoculations are made, and 2) The time of reinoculation in respect to the first or primary infection.

We have considerable data in our notes, not specifically cited here, which can only be explained on the basis of these two factors.

As generally conceived, the reinfection disease is a pathologic process in which the various phases of the disease are all shortened by the influence of the immunologic and allergic processes involved. Its duration is normally 12 to 15 days. It is relatively very inflammatory with severe exfoliation of the affected part. The inflammatory process begins in 18 to 36 hours after inoculation and proceeds rapidly to a peak, in the course of three to four or five days. The scaling begins on the second or third day, becoming progressively more severe, eventually (sixth to seventh day) forming a crust which separates, leaving a wound which may be open to a varying degree, and which heals with further scaling and gradual decline of the inflammatory reaction. This, it is obvious, is distinct from the primary infection.

Fungi are present in the lesions in about 50 per cent of the cases, but persist in those where found for a relatively short time (four to eight days) only. This last represents what we consider as partial immunity.

If we compare this clinical process with that of the primary infection and attempt to subdivide it into phases corresponding to those of the first infection, we find that:

1. The period of incubation is 18 to 36 hours long, shows none or few of the characters of the primary lesion associated with the "take" of the fungi and ends abruptly in:

2. The period of spread, which is precipitate in its inflammatory onset. It is short in duration (three to four days). This is quite different from the corresponding phase of the first infection in which the inflammatory process develops slowly and rises to a peak, and in which the fungi are given an opportunity to grow and the lesion to spread peripherally in characteristic fashion. It is immediately self-limited, while the primary infection becomes gradually self-limited as the whole process develops.

3. It is difficult to define a period corresponding to the climax of the first infection. At most, it must be considered as an integral part of the reactive process just described.

4. The period of clearing begins about the seventh day with exfoliation of the crust and scaling. It simulates more closely the scaling seen in the test papules than that in a primary lesion.

This picture is seen in reinoculations done from approximately the time of climax of the primary disease to about the fifth month after the primary disease has cleared. During this time the allergy and immunity are sufficiently high to prevent any actual infections and to obscure the phases of the disease seen to develop in non-allergic and susceptible animals.

Reinoculations done prior to the climax of the first infection demonstrate very clearly a true telescoping of the four phases of the disease. Each phase is shortened, as is the total duration, proportional to the degree of allergy and immunity developed by the current primary infection. The greater the development of these processes the more rapid the course, the shorter the phases, and the more acute the pathologic change, until the whole second inoculation disease becomes a climactic, extremely acute affair, in which all typical phases are obscured. The processes at work, however, are perfectly apparent if one observes their development (chart 2).

Exactly the same is true if one obscures the effect of a gradual loss of immunity and allergy in the course of second inoculation (chart 4).

There is another factor which affects the reinoculation disease and modifies it clinically. This is the local skin immunity and relative anergy produced by the primary infection in the lesion area. This has already been considered briefly, but is of sufficient importance to be given further consideration.

In the first place, with our *Trichophyton gypseum* (⁂108 strain), it can be produced and demonstrated consistently in the skin area of the primary lesion when this lesion has cleared. Inoculations done in the lesion area (ipsilateral) have a maximum duration of eight to nine days, are relatively uninflammatory and scaly and invariably show complete immunity. Any aberrant results can be ascribed to spreading of the inoculation beyond the limits of the primary lesion.

In contrast, inoculations on non-lesion areas (contralateral)

persist for 15 to 16 days, are always relatively more inflammatory, very scaly and crusted. Fungi may be found up to the eighth day in about 50 per cent of the cases.

These results are important because they probably explain, or at least give an adequate basis for explaining, the inconsistent results of previous authors (2) as well as inconsistent data in our own notes. When considered with reference to the time relationships of the allergy and immunity, already cited, as affecting the course of second inoculations, this topical skin immunity takes on added significance. But it is with respect to the relative anergy of the lesion areas as shown by test injections of extracts and in regard to the general subject of local skin immunity and allergy, as associated with the general bodily processes of immunity and allergy, that it is most important (4). Further studies of these problems are planned.

I. DIFFERENCES IN TEST REACTIONS DONE IN PREVIOUSLY INFECTED AND PREVIOUSLY UNINFECTED SKIN AREAS

Corresponding skin tests were done in previous lesion areas (ipsilateral) and in uninfected skin areas on the same animals. The results are tabulated in chart 5.

It is readily seen that the papules are approximately the same size or slightly larger in the ipsilateral areas, but that the duration is strikingly different. The papules persist for only seven to eight days in the ipsilateral, as contrasted with 15 to 16 days in the contralateral regions. This corresponds directly with the reduced inflammatory reactions observed in ipsilateral reinoculations in contrast with those in the contralateral.

Similar test injections done in reinoculation lesion areas in animals inoculated as many as seven times, show results exactly similar to those just described for the primary lesion skin areas provided an actual "take" or infection has been produced by the reinoculation. For this the immunity produced by the inoculations must be sufficiently low, whether due to an inadequate rise during the previous infections, or to a loss of immunity from elapse of time since the last infection, for a "take" to occur.

The duration of these differences in the allergic and immunologic response of previously infected and previously uninfected skin areas has been adequately followed for a period of only six weeks after the clearing of the lesion. The data in chart 6 plainly show, however, that these differences are as clear cut and

CHART 5

Differences in reinoculations done in previously infected (ipsilateral) and uninfected (contralateral) skin areas

	NUMBER OF ANIMALS	DURATION OF LESION	PRESENCE OF FUNGI	RELATIVE INFLAMMATORY RESPONSE	DEGREE OF SCALING
		days	*days*		
Primary infection (control)	139	32–39	19–30	+	++
Ipsilateral reinoculation	29	8–9	0	+	+
Contralateral reinoculation	29	15–16	±8 (a)–±50% 0 (b)–±50%	+++	+++

CHART 6

Differences in test reactions in previously infected and previously uninfected skin areas

	AFTER THE PRIMARY DISEASE		AFTER REPEATED (2ND TO 7TH)* REINOCULATIONS (WITH TAKE)	
	Ipsilateral test reactions	Contralateral test reactions	Ipsilateral	Contralateral
Number of animals	20	20	16	16
Duration of papule (days)	7–8	15–16	6–7	12–13
Size of papule (cm.)	2+	2	1½	1½–2

* Cases showing divergences from these results can usually be shown to be caused by—a, inadequate knowledge of previous lesion areas, and b, to inadequate "take" or infection to affect the tissue reactions.

striking after six weeks as they are immediately following the infection. How long they will persist and how they may change with the passage of time is still to be determined.

What the course of events is which leads to the production of a complete immunity associated with a reduced allergy (relative

anergy) in the lesion area is not yet clear. The exposure of the tissues directly to the fungus elements and their products may act to speed up within this area the same immunologic processes, which tend to develop much more slowly in the skin not directly exposed to the fungi. This is theoretically possible and plausible, and is suggested by the fact that the lesion area itself progresses through a sequence of stages in which the allergic phenomena (as indicated by the degree of inflammatory response) undergo a gradual rise to a peak and then fall off, while the rest of the

CHART 7

Persistence in the differences of reaction and immunity in previously infected and previously uninfected skin areas

	TIME REINOCULATIONS DONE AFTER PRIMARY									
	1-2 days		1 week		2 weeks		1 month		6 weeks	
	Ipsilateral	Contra-lateral	Ipsilateral	Contra-lateral	Ipsilateral	Contra-lateral	Ipsilateral	Contra-lateral	Ipsilateral	Contra-lateral
Number of animals	20	20	20	20	20	20	20	20	20	20
Duration of papule (days)	8–9	15–16	5	17–18	11	12	11	18	7–8	15–16
Degree of inflammatory response	+	++	±	+++	+	+++	+	+++	±	+++
Degree of crusting in lesions	+	+++	+	+++	+	+++	+	+++	+	+++
Duration of fungi (days)	0	0–8	0	0–5	0	0–5	0	0–5	0	0–5

skin (that uninfected directly with fungi) merely shows the gradual rise of the allergic reactions with no reduction. This is further substantiated by the relatively greater inflammatory reaction of reinoculations done in previously uninfected areas than occurs in either the primary lesion or reinoculations done in previously infected areas.

Data presented in 1938 and to be amplified here on the accentuation of hypersensitivity by repeated inoculations may also be of significance in the interpretation of this problem.

J. ACCENTUATION OF HYPERSENSITIZATION BY REPEATED INOCULATIONS

Previously (2) it was shown that it is possible to increase the general allergic reactivity of guinea pigs to standard test injections (0.2 cc. doses) of homologous Trichophyton extracts by repeatedly inoculating the animals. More recently it has become clear that to achieve this by such methods an actual reinfection must occur from the reinoculation. This requires that the primary immunity developed be sufficiently low so that a "take" occurs. This state can exist from a loss of the immunity over a period of time, or by an insufficient rise of the immunity during the primary infection.

EXPERIMENTAL TRICHOPHYTID

These accentuated hypersensitivity reactions probably do *not* compare to the Trichophytid reactions described by Henrici (8) and observed by ourselves (3) and others (4). They are in the first place developed gradually by repeated inoculations, while the "ids" are developed by a single infection. Furthermore, they are elicited by relatively minute intradermal test doses of fungous extracts, while the "ids" require large, even massive, doses of fungus spores, "cell sap" or crude polysaccharide injected intraperitoneally (8). The "id" reaction is predominantly localized in the skin areas of previous infection (abdominal in Henrici's cases) but may, according to Henrici, extend somewhat beyond the limits of these areas. Reactions occurring on the feet, nose, ears, about the eyes, etc., are probably for the major part, reactions in previous lesion sites as determined by microscopic examination in this laboratory. They should be so considered until proven to be otherwise.

The intradermal test doses in animals with accentuated hypersensitivity will also elicit erythema and scaling in old lesion areas, but in addition, with extreme generalized sensitization, the whole skin becomes erythematous with a subsequent exfoliation (2).

Both the size of the "shocking dose" and the fact that the reactions occur predominantly in previously infected skin sug-

gest implications of considerable importance in appreciating and interpreting human "id" reactions.

Another pertinent difference between these two types of reactions is seen in the fact that the massive doses of antigen used to elicit the "id" lowers the general sensitivity level of the animal injected. This is demonstrated by following the sensitivity curve by intradermal test injections. Chart 8 clearly demonstrates this point. After a sufficient rest or rehabilitation period the degree of sensitization is found to rise again to its previous level.

The small test doses however, which are used to elicit the generalized reactions in animals with accentuated hypersensitivity affect in no way the general level of reactivity.

CHART 8

	NUMBER OF ANIMALS	41ST DAY, 8TH TEST	51ST DAY, 9TH TEST		65TH DAY, 10TH TEST	85TH DAY 11TH TEST
Duration of papule (days)	16*	10–11	15–16	Shock dose	9–10	11–12
Size of papule (cm.)	16*	2	1½+– 2		–1	1+
Duration of papule (days)	2†	10–11	15–16		12–13	11–12
Size of papule (cm.)	2†	2	1½– 2		1½	1+

* Experimental.
† Control.

SUMMARY

The significant features of the material presented here are the following:

1. The allergy (hypersensitivity) to *T. gypseum* is developed only during the course of an infection. It rises gradually during the infection, reaching its peak two to three weeks after the lesions are healed.

2. This hypersensitivity gradually decreases over a period of months after the infection.

3. Immunity to reinfection is established concurrently with

the allergy during the course of the infection, and appears to be closely associated with it.

4. This immunity likewise is found to decline, and loses its ability to protect the animal after a period of some months.

5. Local phenomena of complete immunity associated with a diminished allergy can be demonstrated in the lesion sites. Such a divisibility of the allergy and the immunity may only be apparent or it may be real.

6. So-called "id" reactions and accentuated hypersensitivity are probably distinct phenomena and are developed and elicited in different ways.

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